Complete Summary

GUIDELINE TITLE

Fungal infections. In: Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children.

BIBLIOGRAPHIC SOURCE(S)

Fungal infections. In: Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), HIV Medicine Association of the Infectious Diseases Society of America, Pediatric Infectious Diseases Society, American Academy of Pediatrics. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2008 Jun 20. p. 39-73.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 3;53(RR-14):1-92. [422 references]

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Fungal infections among human immunodeficiency virus (HIV)-exposed and HIV-infected children, including:

- Aspergillosis
- *Candida* infections (including oropharyngeal, esophageal, and invasive)
- Coccidioidomycosis
- Cryptococcosis (including central nervous system [CNS] disease, pulmonary and extrapulmonary cryptococcosis)
- Histoplasmosis (including acute primary pulmonary histoplasmosis, progressive disseminated histoplasmosis [PDH], CNS infection, and asymptomatic histoplasma granuloma)
- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP)

GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Management
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pediatrics
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Clinical Laboratory Personnel
Health Care Providers
Nurses
Patients
Pharmacists
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To provide evidence-based guidelines for treatment and prophylaxis of opportunistic infections among HIV-exposed and HIV-infected children
- To serve as a companion to the United States Public Health Service (USPHS)/Infectious Diseases Society of America (IDSA) *Guidelines for the Prevention of Opportunistic Infections Among HIV-Infected Adults*

TARGET POPULATION

Human immunodeficiency virus (HIV)-exposed and HIV-infected children living in the United States

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention/Counseling

1. Preventing exposure, including counseling on avoidance of exposure and behavior modification
2. Preventing first episode of disease
3. Primary prophylaxis*
    - Discontinuing primary prophylaxis
4. Prevention of recurrence
    - Secondary prophylaxis*
    - Discontinuing secondary prophylaxis

Treatment/Management

1. Antifungal drug therapy*
2. Highly active antiretroviral therapy (HAART)
3. Monitoring and adverse events, including immune reconstitution inflammatory syndrome (IRIS) and raised intracranial pressure
4. Management of treatment failure

*__Note__: Details of antifungal drug therapy and prophylaxis can be found in the "Major Recommendations" section of this summary and in and Tables 1-6 of the original guideline document.

MAJOR OUTCOMES CONSIDERED

- Incidence of fungal infections
- Incidence of invasive disease
- Treatment response
- Adverse drug reactions
- Clinically relevant drug interactions
- Immune reconstitution inflammatory syndrome (IRIS)
- Mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Pediatric specialists with expertise in specific opportunistic infections were selected to review the literature since the last publication of the prevention and treatment guidelines.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence Supporting the Recommendations

I: Evidence from at least one randomized, controlled trial.

II: Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.

III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The current document combines recommendations for prevention and treatment of opportunistic infections (OIs) in human immunodeficiency virus (HIV)-exposed and -infected children into one document; it accompanies a similar document on prevention and treatment of OIs among HIV-infected adults prepared by a separate group of adult HIV and infectious disease specialists. Both sets of guidelines were prepared by the Opportunistic Infections Working Group under the auspices of the Office of AIDS Research (OAR) of the national Institutes for Health. Pediatric specialists with expertise in specific OIs were selected to review the literature since the last publication of the prevention and treatment guidelines, conferred over a period of several months, and produced draft guidelines.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating Scheme for Prevention and Treatment Recommendations

A: Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. **Should always be offered.**

B: Moderate evidence for efficacy - or strong evidence for efficacy but only limited clinical benefit - supports recommendation for use. **Should generally be offered.**

C: Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequence (e.g., drug toxicity, drug interactions) or cost of the treatment or under consideration. **Optional.**

D: Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should generally not be offered.**

E: Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should never be offered.**

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Recommendations were reviewed and discussed by the Pediatric Opportunistic Infections (OI) Working Group at a meeting in Bethesda, Maryland, on June 25–26, 2007. The final document was prepared after this meeting, reflecting the discussion and further revisions at that meeting.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The quality of evidence supporting the recommendations (I-III) and the rating scheme for the recommendations (A-E) are defined at the end of the "Major Recommendations" field.

Refer to the original guideline document for information on epidemiology, clinical manifestations, and diagnosis of fungal infections in human immunodeficiency virus (HIV)-exposed and HIV-infected children.

Fungal Infections: Aspergillosis

Prevention Recommendations

Preventing Exposure

In HIV-infected children who are severely immunosuppressed or neutropenic, considerations for preventing exposure to *Aspergillus* might include excluding plants and flowers from rooms, avoiding food items such as nuts and spices that are often contaminated, and minimizing application of nonsterile biomedical devices and adhesive tape. Other hospital environmental measures that may be effective in preventing aspergillosis outbreaks include structuring suitable barriers between patient care areas and construction sites; routine cleaning of showerheads, hot water faucets, and air handling systems; repair of faulty air flow; confinement of patients to hospital rooms supplied with sterile laminar airflow (LAF); and installation of high-efficiency particulate air (HEPA) filters.

Preventing First Episode of Disease

The use of chemoprophylaxis for aspergillosis is not recommended in HIV-infected children because of the low incidence of invasive disease and the unknown efficacy of potential prophylaxis in children, combined with the potential toxicities of likely agents. Low-dose amphotericin B, itraconazole, or voriconazole prophylaxis has been employed to prevent aspergillosis, with unknown efficacy.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

The recommended treatment for invasive aspergillosis is voriconazole, a second-generation triazole and synthetic derivative of fluconazole. Adult data have shown voriconazole to be superior to conventional amphotericin B in treatment of aspergillosis and that it is associated with superior survival **(AI)**. However, there are only limited data in children.

In immunocompromised children with invasive fungal infection in a compassionate use program of voriconazole, including 42 children with aspergillosis, voriconazole treatment had a complete or partial response in 45% overall, with 43% response in children with aspergillosis. The optimal pediatric dose of voriconazole is not yet known. Children require higher doses (on a mg per kg body weight basis) of voriconazole than adults to attain similar serum concentrations. The recommended dose of voriconazole for children is 6 – 8 mg/kg intravenously or 8 mg/kg orally every 12 hours for two doses, followed by 7 mg/kg intravenously or orally twice daily. For critically ill patients, the parenteral administration is recommended **(AIII)**. Therapy is continued for ≥12 weeks, but treatment duration should be individualized for each patient based on clinical response. Voriconazole has not been studied in HIV-infected children.

Voriconazole is cleared primarily through three key hepatic microsomal cytochrome P450 (CYP450) enzymes, CYP2C19, CYP2C9, and CYP3A4, with most metabolism mediated through CYP2C19. As a result of a point mutation in the

gene encoding CYP2C19, some individuals are poor metabolizers and others are extensive metabolizers; about 3% – 5% of white and African human populations are poor metabolizers, while 15% – 20% of Asian populations are poor metabolizers. Drug levels can be as much as 4-fold greater in poor metabolizers than in individuals who are homozygous extensive metabolizers. Coadministration of voriconazole with drugs that are potent CYP450 enzyme inducers can significantly reduce voriconazole levels. Voriconazole should be used cautiously with HIV protease inhibitors (PIs) and efavirenz because of potential interactions, and consideration given to therapeutic drug monitoring if used concomitantly **(CIII)**.

Amphotericin B, either conventional or a lipid formulation, is an alternative regimen **(AIII)**. The standard amphotericin B deoxycholate dose is 1.0 – 1.5 mg/kg/day. Lipid formulations of amphotericin B allow administration of higher dosage, deliver higher tissue concentrations of drug to reticuloendothelial organs (e.g., lungs, liver, spleen), have fewer infusion-related side effects and less renal toxicity, but are more expensive; dosing of 5 mg/kg/day is recommended.

Surgical excision of a localized invasive lesion may be warranted, especially in sinus aspergillosis, certain cases of pulmonary aspergillosis with impingement on great vessels or pericardium, those with hemoptysis from a single focus, and those with erosion into the pleural space or ribs **(BIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

The main side effects of voriconazole include reversible dose-dependent visual disturbances (increased brightness, blurred vision) in about a third of patients, elevated hepatic transaminases with higher doses, and occasional skin rash; as noted earlier, interactions with PIs and efavirenz can be a problem. The primary toxicities of amphotericin B include infusion-related fever/chills and nephrotoxicity.

Patients should be monitored for adverse effects related to antifungal agents, especially amphotericin B. Only one case of aspergillosis-associated immune reconstitution inflammatory syndrome (IRIS) has been described.

Management of Treatment Failure

The efficacy of antifungal therapy in invasive aspergillosis has been extremely poor. No data are available to guide recommendations for the management of treatment failure. For patients who had failed treatment or were unable to tolerate voriconazole, amphotericin B should be considered **(BIII)**. Itraconazole for aspergillosis refractory to primary therapy with voriconazole is not recommended due to the similar mechanisms of action and possible cross resistance **(DIII)**.

Caspofungin is approved for adults with invasive aspergillosis who fail to improve or are intolerant of standard therapy, and could be considered for treatment failure in children, although there are limited data on this drug in children. In a pharmacokinetic study in 39 children aged 2 to 12 years, dosing on a body surface area basis was recommended over a weight-based dosing scheme; a dose of 50 mg/meter^2 body surface area once daily resulted in area under the curve

concentrations similar to exposure in adults receiving the standard dose of 50 mg/day. Due to limited bioavailability, caspofungin is only available for intravenous use.

Combination therapy with caspofungin and voriconazole has been studied in a small number of adults and children with invasive aspergillosis. In the setting of salvage therapy, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than the initial regimen may be used **(BIII)**.

Prevention of Recurrence

For patients with non-HIV-related immunosuppression, continuation of antifungal therapy throughout the duration of immunosuppression seems to be associated with a more favorable outcome in other patient populations. However, no data are available in HIV-infected populations, and hence no recommendations can be made for or against secondary prophylaxis **(CIII)**.

Discontinuing Secondary Prophylaxis

Not applicable.

Fungal Infections: *Candida* Infections

Prevention Recommendations

Prevention of Exposure

Candida organisms are common commensals on mucosal surfaces in healthy individuals, and no measures are available to reduce exposure to these fungi.

Prevention of First Episode of Disease

Routine primary prophylaxis of candidiasis among HIV-infected infants and children is not indicated, given the low prevalence of serious *Candida* infections (e.g., esophageal, tracheobronchial, disseminated) in the highly active antiretroviral therapy (HAART) era and the availability of effective treatment. There are also concerns regarding potential development of resistant *Candida* strains, drug interactions between antifungal agents and antiretrovirals, and the lack of randomized controlled trials in the pediatric population **(DIII)**.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

Oropharyngeal Candidiasis

Early, uncomplicated infection can be effectively treated with topical therapy using clotrimazole troches or oral polyenes (such as nystatin or amphotericin B suspension) **(BII)**. Troches should not be used in infants **(DIII)**. Resistance to clotrimazole can develop as a consequence of previous exposure to clotrimazole itself or to other azole drugs; resistance correlates with refractory mucosal candidiasis.

Systemic therapy with one of the oral azoles (e.g., fluconazole, ketoconazole, or itraconazole) is also effective for initial treatment of oropharyngeal candidiasis (OPC). Oral fluconazole is more effective than nystatin suspension for initial treatment of OPC in infants, is easier to administer to children than the topical therapies, and is the recommended treatment if systemic therapy is used **(AI)**.

Itraconazole solution is comparable in efficacy to fluconazole and can also be used to treat OPC, although it is less well tolerated than fluconazole **(AI)**. Absorption of itraconazole solution is enhanced by the presence of gastric acid; it should be taken without food when possible. Itraconazole capsules and oral solution should not be used interchangeably because drug exposure is greater with the oral solution when the same dose of drug is administered and absorption of the capsule formulation is variable. Ketoconazole absorption is also variable, and therefore neither itraconazole capsules nor ketoconazole are recommended for treatment of OPC if fluconazole or itraconazole solutions are available **(DII)**.

Esophageal Disease

Systemic therapy is essential for esophageal disease **(AI)** and should be initiated empirically among HIV-infected children with OPC and esophageal symptoms. In most patients, symptoms should resolve within days of the start of effective therapy. Oral or intravenous fluconazole or oral itraconazole solutions, given for 14 to 21 days, are highly effective for treatment of *Candida* esophagitis **(AI)**. As for OPC, ketoconazole and itraconazole capsules are not recommended for treatment because of variable absorption and lower efficacy **(DII)**.

Voriconazole, a newer azole antifungal, or caspofungin, an echinocandin inhibitor of fungal (1,3)-beta-D-glucan synthetase that must be given intravenously due to limited bioavailability, are also effective in treating esophageal candidiasis in HIV-infected adults **(BI)**, but there is less experience with these drugs in children. Voriconazole has been used in a limited number of children without HIV infection to treat invasive fungal infections, including some with esophageal candidiasis or candidemia. Voriconazole was generally initially administered intravenously and changed to oral administration to complete therapy after the child had stabilized. The optimal pediatric dose of voriconazole is not yet known; children require higher doses (on a mg/kg body weight basis) than adults to attain similar serum voriconazole concentrations. The recommended voriconazole dose for children is 6 – 8 mg/kg intravenously or 8 mg/kg orally every 12 hours. However, extrapolations from a pharmacokinetic study of voriconazole in immunocompromised children without HIV infection suggests that children may need a dose as high as 11 mg/kg administered every 12 hours to achieve concentrations similar to the adult dose of 4 mg/kg every 12 hours, although doses this high have not been studied. A pharmacokinetic study of caspofungin in immunocompromised children aged 2 to 17 years without HIV infection demonstrated that a dose of 50 mg/meter^2 body surface area/day (70 mg/day

maximum) provides comparable exposure to that obtained in adults receiving a standard 50-mg daily regimen. Because of limited experience with both of these drugs in children, data are insufficient to recommend use of voriconazole or caspofungin as first-line therapy for esophageal or disseminated candidiasis **(CIII)**.

Invasive Disease

Central venous catheters should be removed when feasible in HIV-infected children with candidemia **(AII)**.

Conventional amphotericin B (sodium deoxycholate complex) is the drug of choice for most invasive *Candida* infections in children, given once daily intravenously over 1 to 2 hours **(AI)**. In patients with azotemia, hyperkalemia, or who are receiving high doses (>1 mg/kg), a longer infusion time of 3 to 6 hours is recommended **(BIII)**. In children with life-threatening disease, the target daily dose of amphotericin B should be administered from the beginning of therapy **(BIII)**. Duration of therapy in treatment of candidemia should be determined by the presence of deep tissue foci, patient clinical response, and presence of neutropenia. Patients at high risk for morbidity and mortality should be treated until all signs and symptoms of infection have resolved. Treatment is recommended until 2 to 3 weeks after the last positive blood culture and signs and symptoms have resolved **(AIII)**. Among patients with persistent candidemia despite appropriate therapy, investigation for a deep tissue focus of infection should be conducted (e.g., echocardiogram, renal or abdominal ultrasound). Flucytosine has been used in combination with amphotericin B in some patients with severe invasive candidiasis, particularly in patients with central nervous system (CNS) disease **(CIII)**, but has a narrow therapeutic index.

Fluconazole has been used as an alternative to amphotericin B for treatment of invasive disease in those who have not recently received azole therapy **(AI)**. Treatment of invasive candidiasis requires higher doses of fluconazole than are used for mucocutaneous disease. Alternatively, an initial course of amphotericin B therapy can be administered and then carefully followed by completion of a course of fluconazole therapy **(BIII)**. Species identification is necessary when using fluconazole due to intrinsic drug resistance among certain *Candida* species (e.g., *C. krusei* and *C. glabrata*) **(EIII)**. Fluconazole given to children at 12 mg/kg/day provides exposure similar to standard 400 mg daily dosing in adults. Clearance in older adolescents can be similar to adults, so dosing above 600 mg/day should be employed with caution.

Antifungal agents in the echinocandin class including caspofungin, micafungin, and anidulafungin have been studied in adults with HIV infection, neutropenic children at risk of fungal infections, and children with documented candidiasis. Due to limited experience in children and no data in HIV-infected children, data are insufficient to recommend these drugs as first-line agents for invasive candidiasis in children **(CIII)**. The use of caspofungin in children with systemic candidiasis is limited. In a retrospective report in which caspofungin was administered to 20 children aged 0.1 to 16 years with invasive fungal infections (7 had invasive candidiasis) but without HIV infection, the drug was efficacious and well tolerated. In a study of 10 neonates with persistent and progressive candidiasis and unknown HIV status, caspofungin was reported to be effective alternative therapy.

Micafungin has been studied in HIV-uninfected, neutropenic children at risk of invasive fungal infections. This drug demonstrates dose-proportional pharmacokinetics and an inverse relationship between age and clearance, suggesting a need for increased dosage in the young child. A study of 19 Japanese HIV-uninfected children aged 0.6 to 15 years with confirmed invasive fungal infections, such as candidiasis, showed that plasma concentration of micafungin dosed at 3 mg/kg body weight was similar to that in adults given 150 mg per dose. Micafungin was administered to premature infants who were receiving antifungal therapy for a suspected invasive fungal infection. Clearance of the drug in neonates was more than double the clearance in older children and adults. Dosages of 10 – 15 mg/kg/day have been studied in premature neonates, resulting in area under the curve values consistent with an adult dose of 100–150 mg/day. One pharmacokinetic study of anidulafungin in HIV-uninfected neutropenic children aged 2 to 17 years showed drug concentrations at doses of 0.75 mg/kg per dose and 1.5 mg/kg per dose were similar to drug concentrations observed in adults with doses of 50 mg per dose and 100 mg per dose, respectively.

There are limited data in adults on use of combination antifungal therapy for invasive candidal infections; combination amphotericin B and fluconazole resulted in more frequent clearance of *Candida* from the bloodstream but no difference in mortality. There are insufficient data to support the routine use of combination therapy in children with invasive candidiasis **(DIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

No adverse effects have been reported with the use of oral nystatin for treatment of oral candidiasis, but bitter taste might contribute to poor adherence.

The azole drugs have relatively low rates of toxicity but because of their ability to inhibit the CYP450-dependent hepatic enzymes (ketoconazole has the strongest inhibitory effect) they can have substantial interactions with other drugs undergoing hepatic metabolism. These interactions can result in decreased plasma concentration of the azole because of increased metabolism induced by the coadministered drug, or development of unexpected toxicity from the coadministered drug because of increased plasma concentrations secondary to azole-induced alterations in hepatic metabolism. The potential for drug interactions, particularly with antiretroviral drugs such as PIs, should be carefully evaluated before initiation of therapy **(AIII)**.

The most frequent adverse effects of the azole drugs are gastrointestinal, including nausea and vomiting (10%–40% of patients). Skin rash and pruritus might be observed with all drugs; rare cases of Stevens-Johnson syndrome and alopecia have been reported with fluconazole therapy. All drugs are associated with asymptomatic increases in transaminases (1%–13% of patients) and, less frequently, hepatitis. Hematologic abnormalities have been reported with itraconazole, including thrombocytopenia and leukopenia. Of the azoles, ketoconazole is associated with the highest frequency of side effects. Its use has been associated with endocrinologic abnormalities related to steroid metabolism, including adrenal insufficiency and gynecomastia, hemolytic anemia, and transaminitis. Dose-related, reversible visual changes (e.g., photophobia and

blurry vision) have been reported in approximately 30% of patients receiving voriconazole. Cardiac arrhythmias and renal abnormalities including nephritis and acute tubular necrosis also have been reported with voriconazole use.

Amphotericin B deoxycholate undergoes renal excretion as inactive drug. Adverse effects of amphotericin B are primarily nephrotoxicity, defined by substantial azotemia from glomerular damage, and can be accompanied by hypokalemia from tubular damage. Nephrotoxicity is exacerbated by use of concomitant nephrotoxic drugs. Permanent nephrotoxicity is related to cumulative dose. Nephrotoxicity can be ameliorated by hydration with 0.9% saline intravenously over 30 minutes before the amphotericin B infusion. Infusion-related fevers, chills, nausea, and vomiting can occur, although they are less frequent in children than in adults. Onset is usually within 1 to 3 hours after the infusion is started, typical duration is <1 hour, and the febrile reactions tend to decrease in frequency over time. Pretreatment with acetaminophen or diphenhydramine might alleviate febrile reactions. Idiosyncratic reactions including hypotension, arrhythmias, and allergic reactions, including anaphylaxis, occur less frequently. Hepatic toxicity, thrombophlebitis, anemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) also can occur.

Lipid formulations of amphotericin B can cause acute, infusion-related reactions in approximately 20% of patients, including chest pain; dyspnea; hypoxia; severe abdomen, flank, or leg pain; or flushing and urticaria. Compared with infusion reactions with conventional amphotericin B, most of the reactions to the lipid formulations (85%) occur within the first 5 minutes of infusion and rapidly resolve with temporary interruption of the amphotericin B infusion and administration of intravenous diphenhydramine. Premedication with diphenhydramine can reduce the incidence of these reactions.

Flucytosine has considerable toxicity: its effect on the bone marrow (e.g., anemia, leukopenia, thrombocytopenia), liver, GI tract, kidney, and skin warrants close monitoring of drug levels and dose adjustment to keep the level between 40–60 micrograms/mL. Therapeutic drug monitoring should be employed with this product, especially in patients with renal impairment. High levels can result in bone marrow suppression. The drug should be avoided in children with severe renal impairment **(EIII)**.

The echinocandins have an excellent safety profile. In a retrospective evaluation of 25 immunocompromised children who received caspofungin, the drug was well tolerated and only 3 patients had adverse events that might have been related to the drug (hypokalemia in all 3 children, elevated bilirubin in 2, and decreased hemoglobin and elevated alanine aminotransferase in 1). In this study, children weighing <50 kg received doses ranging from 0.8–1.6 mg/kg body weight daily, and those weighing >50 kg received adult dosing. In the pharmacokinetic study of 39 children who received caspofungin at a dose of 50 mg/meter^2 body surface area/day, 5 (12.8%) patients experienced ≥1 drug-related clinical adverse event, including 1 patient each with fever, diarrhea, phlebitis, proteinuria, and transient extremity rash. Two patients reported ≥1 drug-related laboratory adverse event, including 1 patient each with hypokalemia and increased serum aspartate transaminase. None of the drug-related adverse events in this study were considered serious or led to discontinuation of caspofungin.

IRIS due to *Candida* infection has not been described in children; however, there may be evidence suggesting that candidiasis occurs with increased frequency in adults during the first 2 months after initiating HAART, with the exception of candidal esophagitis.

Management of Treatment Failure

Oropharyngeal and Esophageal Candidiasis

If initial therapy of OPC is with topical therapy, failure or relapse should be treated with oral fluconazole or itraconazole cyclodextrin oral solution **(AI)**.

Approximately 50%–60% of patients with fluconazole-refractory OPC and 80% of patients with fluconazole-refractory esophageal candidiasis will respond to itraconazole solution **(AII)**. Posaconazole is a second-generation orally bioavailable triazole that has been effective in HIV-infected adults with azole-refractory OPC and/or esophageal candidiasis. However, experience in children is limited and appropriate pediatric dosage has not been defined; thus there are insufficient pediatric data to recommend its use in HIV-infected children **(CIII)**.

Amphotericin B oral suspension at a dose of 1 mL 4 times a day of a 100 mg/mL suspension has sometimes been effective among patients with OPC who do not respond to itraconazole solution; however, this product is not available in the United States **(CIII)**. Low-dose intravenous amphotericin B (0.3 - 0.5 mg/kg/day) has been effective among patients with refractory OPC or esophageal candidiasis **(BII)**.

There is very limited experience with the use of echinocandins in the treatment of azole-refractory OPC or esophageal candidiasis in children (with or without HIV infection); however, given their excellent safety profile, the two echinocandins with the most pediatric data, caspofungin or voriconazole, could be considered for treatment of azole-refractory esophageal candidiasis **(CIII)**.

Invasive Disease

Amphotericin B lipid formulations have a role among children who are intolerant of amphotericin B, have disseminated candidal infection that is refractory to conventional amphotericin B, or are at high risk for nephrotoxicity because of pre-existing renal disease or use of other nephrotoxic drugs **(BII)**. Although lipid formulations appear to be at least as effective as conventional amphotericin B for treatment of serious fungal infections, the drugs are considerably more expensive than conventional amphotericin B. Two lipid formulations are currently used, including amphotericin B lipid complex (ABELCET) and liposomal amphotericin B lipid complex (AmBisome). Experience with these preparations among pediatric patients is limited.

For invasive candidiasis, amphotericin B lipid complex (ABELCET) is administered as 5 mg/kg body weight once daily given over 2 hours intravenously. Amphotericin B liposome (AmBisome) is administered as 3–5 mg/kg body weight once daily over 1 to 2 hours intravenously. Duration of therapy is based on clinical response; most patients are treated for at least 2 to 4 weeks.

The role of the echinocandins in invasive candidiasis has not been well studied in HIV-infected children; however, neutropenic patients undergoing bone marrow transplantation have been successfully treated with this class of antifungals. These agents should be considered in the treatment of invasive candidiasis, but reserved as alternative, second-line therapy to currently available treatment modalities **(CIII)**.

Prevention of Recurrence

Secondary prophylaxis of recurrent OPC is generally not recommended because (1) treatment of recurrence is generally effective, (2) the potential exists for the development of resistance, (3) the issue of drug interactions, and (4) cost **(DIII)**. Immune reconstitution with HAART in children who are immunocompromised should be a priority **(AIII)**. However, if recurrences are severe, based on data in HIV-infected adults with advanced disease on HAART, suppressive therapy with systemic azoles, either oral fluconazole **(BI)** or itraconazole solution **(CI)**, can be considered. Potential azole resistance should be considered when long-term prophylaxis with azoles is considered.

Based on data in HIV-infected adults, in children with fluconazole-refractory OPC or esophageal candidiasis who have responded to voriconazole or posaconazole therapy or echinocandins, continuing the effective drug as secondary prophylaxis may be considered because of high relapse rate until HAART produces immune reconstitution **(CI)**.

Discontinuing Secondary Prophylaxis

In situations where secondary prophylaxis is instituted, there are no data on which to base a recommendation regarding discontinuation, but it would be reasonable based on experience with HIV-infected adults with other opportunistic infections (OIs) to discontinue secondary prophylaxis when the CD4 count or percentage has risen to Centers for Disease Control and Prevention (CDC) Immune Class 2 or 1.

Fungal Infections: Coccidioidomycosis

Prevention Recommendations

Preventing Exposure

Although HIV-infected persons residing in or visiting regions in which coccidioidomycosis is endemic cannot completely avoid exposure to *Coccidioides* spp., exposure risk can be reduced by avoidance of activities that predispose to inhalation of spores. Such activities include disturbing contaminated soil, excavation of archaeological sites, and/or being outdoors during dust storms. If such activities are unavoidable, respiratory filtration devices should be considered.

Preventing First Episode of Disease

No prospective studies that examine the role of primary prophylaxis to prevent development of active coccidioidomycosis have been published. Although some

experts would provide primary prophylaxis with an azole (e.g., fluconazole) to coccidioidal antibody-positive HIV-infected patients living in an endemic region, other experts would not. Some experts would consider chemoprophylaxis for coccidioidal antibody-positive HIV-infected individuals considered at higher risk for development of active disease, including African Americans, those with unreconstituted cellular immunity with CD4 counts <250 cells/mm^3, and those with a history of thrush **(CII)**. However, given the low incidence of coccidioidomycosis in pediatric HIV-infected patients, possibility of drug interactions, potential antifungal drug resistance, and cost, routine use of antifungal medications for primary prophylaxis of coccidioidal infections in children is not recommended.

Routine skin testing of HIV-infected patients with coccidioidin (spherulin) is not predictive of infection and should not be performed **(CIII)**.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

All patients with HIV infection who receive a diagnosis of clinically active coccidioidomycosis should be offered antifungal therapy. Treatment protocols for HIV-infected children are based on experience with adults in nonrandomized open-label studies. Physicians who infrequently treat children with coccidioidomycosis should consider seeking consultation from experts.

Because the critical factor in the control of coccidioidomycosis is cellular immune function, institution of effective antiretroviral therapy is also important in the treatment of disease and should be done contemporaneously with the initiation of antifungal therapy, if possible.

Diffuse pulmonary or disseminated infection should be treated with amphotericin B deoxycholate at a dose of 0.5 – 1.0 mg/kg/day **(AII)**. Amphotericin B treatment is continued until clinical improvement is observed. The dose and duration of amphotericin B depend on the severity of the symptoms, toxicity, and the rapidity of response. Total doses of amphotericin B deoxycholate in adults have ranged from 10 to 100 mg/kg. Thereafter, amphotericin B may be discontinued and treatment with fluconazole or itraconazole begun **(BIII)**. Some experts initiate therapy with amphotericin B combined with a triazole such as fluconazole in patients with disseminated severe disease and continue the triazole after amphotericin B is stopped **(BIII)**. The total duration of therapy should be ≥1 year.

No clinical evidence supports greater efficacy of the lipid formulations of amphotericin B compared to deoxycholate. However, they are preferred when nephrotoxicity is of concern **(BI)**. A dose of 5 mg/kg/day is recommended for amphotericin B lipid complex and 3 – 5 mg/kg/day for liposomal amphotericin B.

For patients with mild disease (such as focal pneumonia), monotherapy with fluconazole or itraconazole is appropriate given their safety, convenient oral dosing, and pharmacodynamic parameters **(BII)**. Thus, fluconazole (5–6 mg/kg/dose twice daily) or itraconazole (5–10 mg/kg/dose twice daily for 3 days followed by 2 – 5 mg/kg/dose twice daily) are alternatives to amphotericin B for children with mild, nonmeningitic disease **(BIII)**. In a randomized, double-blind trial in adults, fluconazole and itraconazole were equivalent in the treatment of nonmeningeal coccidioidomycosis. However, there was a trend toward itraconazole being superior for skeletal infections **(AI)**.

Meningitis is distinct from other forms of coccidioidal infection, as an antifungal with CNS penetration is needed; thus, intravenous amphotericin B should not be used for coccidioidal meningitis. The relative safety and comparatively superior ability of fluconazole to penetrate the blood-brain barrier have made it the azole of choice for coccidioidal meningitis **(AII)**. Doses of fluconazole found to be effective in adults are 400 mg/day **(AII)**, but some experts begin therapy with 800–1,000 mg/day **(BIII)**. Children usually receive dosages of 5–6 mg/kg/dose twice daily (800 mg/day maximum) **(AII)**. Doses as high as 12 mg/kg/day have been used **(CII)**. This dose is required to achieve serum concentrations equivalent to the adult dosing of 400 mg/day.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

In addition to monitoring the patient for clinical improvement, monitoring coccidioidal complement fixation (CF) immunoglobulin G (IgG) antibody titers is useful in assessing response to therapy. Titers should be obtained every 12 weeks **(AIII)**. A progressive decrease should be seen if therapy is succeeding, and a rise in titers suggests a recurrence of clinical disease. However, patients with serologic test results that were initially negative may have a delayed improvement in their serologic test results that do not correlate with clinical status. This lag in response, occurring during the first 1 or 2 months of therapy, should not be construed as treatment failure.

Adverse effects of amphotericin B are primarily nephrotoxicity. Infusion-related fevers, chills, nausea, and vomiting can also occur, although they are less frequent in children than in adults. Lipid formulations of amphotericin B have lower rates of nephrotoxicity. Hepatic toxicity, thrombophlebitis, anemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) also can occur (see discussion on Monitoring and Adverse Events in "*Candida* Infection" above).

Triazoles may interact with CYP450-dependent hepatic enzymes, and the potential for drug interactions should be evaluated carefully before initiation of therapy **(AIII)**. Fluconazole and itraconazole appear to be safe in combination with antiretroviral therapy. Voriconazole should be avoided in patients receiving HIV PIs or non-nucleoside reverse transcriptase inhibitors (NNRTIs). The most frequent adverse effects of fluconazole are gastrointestinal, including nausea and vomiting. Skin rash and pruritis might be observed, and rare cases of Stevens-Johnson syndrome have been reported. Asymptomatic increases in transaminases can be observed in 1% – 13% of patients receiving azole drugs. In HIV-infected patients, fluconazole at high doses may cause adrenal insufficiency.

Reports of coccidioidomycosis disease in response to IRIS have not been described in children.

Management of Treatment Failure

Limited clinical information is available for newer therapeutic agents. Posaconazole was shown to be effective in six patients with disease refractory to treatment with azoles and amphotericin B **(CII)**. Voriconazole was effective in treating coccidioidal meningitis and nonmeningeal disseminated disease in patients who failed to respond to fluconazole and/or were intolerant of amphotericin B. Caspofungin alone was successful in treating disseminated coccidioidomycosis in a renal transplant patient intolerant of fluconazole and in individuals who have failed conventional therapy. Others have used caspofungin in combination with fluconazole.

Adjunctive interferon-gamma was successfully used in a critically ill adult with respiratory failure who failed to respond to amphotericin B preparations and fluconazole. However, there are no controlled clinical studies or data in children, so it is not recommended for use in HIV-infected children **(DIII)**.

Patients with coccidioidal meningitis who fail to respond to treatment with the azoles may improve with both systemic amphotericin B and direct instillation of amphotericin B into the intrathecal, ventricular, or intracisternal spaces with or without concomitant azole treatment **(CI)**. The basilar inflammation characteristic of coccidioidal meningitis commonly results in obstructive hydrocephalus necessitating the placement of a cerebrospinal fluid (CSF) shunt. The development of hydrocephalus in coccidioidal meningitis is not necessarily indicative of treatment failure.

Prevention of Recurrence

Relapse can occur in as many as 33% of patients with disseminated coccidioidomycosis even in the absence of HIV infection, so lifelong antifungal suppression with either fluconazole or itraconazole is recommended for HIV-infected children with coccidioidomycosis **(AII)**. In coccidioidal meningitis, excellent response rates to the azoles can be achieved, but cures are infrequent and relapse after cessation of therapy is common, occurring in as much as 80% of patients. Thus, it is recommended that fluconazole therapy be continued indefinitely in patients with coccidioidal meningitis **(AII)**.

Discontinuing Secondary Prophylaxis

As with other disseminated fungal infections, continued suppressive therapy with fluconazole or itraconazole is recommended following completion of initial therapy. Patients with diffuse pulmonary disease, disseminated, or meningitic disease should remain on lifelong prophylaxis even if immune reconstitution is achieved with HAART because of high risk of relapse **(AIII)**. In HIV-infected adults with focal coccidioidal pneumonia who have clinically responded to antifungal therapy and have sustained CD4 count >250 cells/mm^3 on HAART, some experts would discontinue secondary prophylaxis after 12 months of therapy with careful monitoring for recurrence with chest radiographs and coccidioidal serology **(CIII)**. However, the numbers of patients who have been evaluated are small and the

safety of discontinuation of secondary prophylaxis after immune reconstitution with HAART among children has not been studied extensively. Therefore, for coccidioidomycosis among HIV-infected children, lifelong suppressive therapy is recommended after an acute episode of the disease, regardless of HAART therapy and immune reconstitution **(AIII)**.

Fungal Infections: Cryptococcosis

Prevention Recommendations

Preventing Exposure

There are no proven strategies for preventing exposure. *Cryptococcus (C.) neoformans* infection is believed to be acquired via inhalation of aerosolized particles from the environment. Serologic studies of immunocompetent children in an urban setting indicate that most children are infected by *C. neoformans* after the second year of life.

Preventing First Episode of Disease

Because the incidence of cryptococcal disease is so low in HIV-infected children, routine testing of asymptomatic persons for serum cryptococcal antigen is not recommended **(DIII)**. Additionally, given the low incidence of cryptococcosis in pediatric HIV-infected patients, lack of survival benefits in adult primary prevention studies, possibility of drug interaction, potential antifungal drug resistance, and cost, routine use of antifungal medications for primary prophylaxis of cryptococcal infections in children is not recommended.

A Cochrane Review of randomized controlled trials using antifungal interventions for the primary prevention of cryptococcal diseases indicates that fluconazole and itraconazole can reduce the frequency of cryptococcal disease among adult patients who have advanced HIV disease and severe immune suppression (CD4 count <50 cells/mm^3). However, neither of these interventions showed a clear effect on mortality.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

Given the low incidence of cryptococcosis in HIV-infected children even in the pre-HAART era, management of this disease in this patient population has not been prospectively studied. Treatment recommendations reflect information extrapolated from many well-designed studies involving HIV-infected adults with cryptococcal meningitis.

Unlike immunocompetent hosts, in whom recovery from pulmonary infection without antifungal treatment can occur, immunocompromised hosts with

cryptococcosis require treatment, since the condition is often fatal in the absence of treatment. Although antifungal treatment is effective, immune reconstitution of the host with the use of antiretroviral medications is crucial to the long-term outcome in terms of avoidance of episodes of recurrence and relapse. However, IRIS can be problematic in the short term, posing a diagnostic dilemma when it presents as clinical worsening in a host that was (or is being) treated appropriately for cryptococcal infection. Although limited data are available on how best to prevent and manage IRIS, because of the close proximity of diagnosis of OIs and initiation of HAART in patients who developed IRIS, some clinicians consider delaying initiation of HAART in treatment-naïve patients who have treatable OIs until after the acute phase of initial OI therapy has been completed. Factors other than IRIS, such as tolerability of OI treatments and HAART and overlapping toxicities if both are started concurrently, are also reasons for delaying HAART initiation. There have been no clinical trials to assess optimal timing of initiation of HAART in patients with concurrent cryptococcosis. Overall *in vitro* resistance to antifungal agents used in the treatment of cryptococcosis remains uncommon. Newer azoles (e.g., voriconazole, posaconazole, ravuconazole) are all very active *in vitro* against *C. neoformans*, but there is limited published clinical experience of using them for cryptococcosis.

CNS Disease

The most common and well-studied presentation of cryptococcal infection in HIV-infected patients is CNS disease. In light of adult studies, combination therapy with amphotericin B and flucytosine for 2 weeks (induction therapy) followed by fluconazole for a minimum of 8 weeks (consolidation therapy) is recommended for pediatric patients **(AI)**. Cryptococci were cleared from CSF significantly more rapidly from adults with CNS disease who received initial therapy with amphotericin B (0.7 mg/kg/day) and flucytosine (100 mg/kg/day) compared with those who received amphotericin B alone, amphotericin B plus fluconazole, or triple-antifungal therapy. In one adult study, liposomal amphotericin B (AmBisome) dosed at 4 mg/kg/day resulted in significantly earlier cerebrospinal fluid (CSF) culture conversion than did amphotericin B at 0.7 mg/kg/day. Although cost differences associated with the formulation of amphotericin B influence the selection of one preparation over another, the liposomal preparation is preferred for patients with renal insufficiency **(AII)**. Monitoring for and managing raised intracranial pressure is crucial to the optimal management of CNS cryptococcosis (see below).

In patients who cannot tolerate flucytosine, amphotericin B (or its liposomal preparation) alone can be used for initial therapy **(BI)**. Fluconazole plus flucytosine is superior to fluconazole alone and provides an alternative to amphotericin B for acute therapy of invasive disease **(BII)**; however, few data are available regarding the use of this combination in children and it should only be used if amphotericin B-based therapy is not tolerated **(BIII)**. Although fluconazole monotherapy was an effective alternative to amphotericin B in adults with acquire immunodeficiency syndrome (AIDS)-associated cryptococcal meningitis, concerns in this study about differences in early death, delayed CSF sterilization, and drug resistance make fluconazole monotherapy a less favorable option for initial therapy of CNS disease. Due to rapid development of resistance, flucytosine alone should never be used for treatment of cryptococcosis **(EII)**.

After a minimum of 2 weeks of induction therapy with evidence of clinical improvement and a negative CSF culture following repeat lumbar puncture, amphotericin B and flucytosine can be discontinued and consolidation therapy initiated with fluconazole **(AI)**. Consolidation therapy is continued for a minimum of 8 weeks. Itraconazole is an alternative to fluconazole for the consolidation phase of CNS therapy and for secondary prophylaxis **(BI)**. Fluconazole is preferred because studies comparing the two agents demonstrate higher rates of CSF sterilization during consolidation therapy and less frequent relapse during maintenance therapy in fluconazole recipients.

Pulmonary and Extrapulmonary Cryptococcosis (CNS Disease Ruled Out)

There are no controlled clinical studies describing the outcome of non-CNS cryptococcosis in HIV-infected patients. CNS disease should be ruled out in all patients, after which the choice of antifungal medication and length of initial therapy can be decided in light of the clinical severity of illness. Patients with severe pulmonary disease or disseminated cryptococcosis should be treated with amphotericin B with or without the addition of flucytosine, as for CNS disease **(AIII)**. In general, combination therapy should be provided until symptoms resolve. Mild-to-moderate pulmonary illness or other localized disease can be managed with fluconazole monotherapy **(AIII)**. Regardless of the antifungal agent selected for initial therapy, suppressive therapy with fluconazole or itraconazole should be continued long term. Discontinuation of secondary prophylaxis can be considered in select cases (see note below on discontinuing secondary prophylaxis).

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Monitoring for Raised Intracranial Pressure

Whenever a lumbar puncture is performed, opening pressure should be measured **(AII)**. Adult studies clearly show the role of increased intracranial pressure in mortality associated with CNS cryptococcosis. Health care providers should be vigilant regarding this condition. Its management includes repeated lumbar punctures. In rare cases, CSF shunting may need to be considered for patients who do not tolerate daily lumbar punctures or if signs and symptoms of cerebral edema are not being relieved with standard management. Corticosteroids and acetazolamide should not be used for reduction of intracranial pressure in cryptococcal meningitis **(DIII)**; acetazolamide was associated with severe acidosis, hypokalemia, and other adverse effects in a clinical trial among adults.

Monitoring for Treatment Response

In addition to monitoring clinical response, mycologic response in patients with CNS cryptococcosis typically is assessed by a repeat lumbar puncture and CSF exam at 2 weeks, with continuation of induction therapy if the culture is positive until negative cultures are obtained.

Monitoring serial serum cryptococcal antigen titers is not useful for following treatment efficacy, because changes in serum cryptococcal antigen titers do not correlate well with outcome during treatment for acute meningitis or during

suppressive therapy. Serial measurement of CSF cryptococcal antigen is more useful; in one study, an unchanged or increased titer of antigen in CSF was correlated with clinical and microbiological failure to respond to treatment and a rise in CSF antigen titer during suppressive therapy was associated with relapse of cryptococcal meningitis. However, monitoring of CSF cryptococcal antigen levels requires repeated lumbar punctures and is not routinely recommended for monitoring response.

Monitoring for Adverse Events

Adverse effects of amphotericin B (Table 5 in the original guideline document) are primarily nephrotoxicity; permanent nephrotoxicity is related to cumulative dose. Infusion-related fevers, chills, nausea, and vomiting can occur, although they are less frequent in children than in adults. Close monitoring for drug toxicities is needed, especially when amphotericin B is used with flucytosine.

Flucytosine has the potential for marked toxicity, especially affecting the bone marrow (e.g., anemia, leukopenia, and thrombocytopenia), liver, gastrointestinal (GI) tract, kidney, and skin. Patients receiving flucytosine should have flucytosine blood levels monitored to prevent bone marrow suppression and GI toxicity; peak serum levels, which occur 2 hours after an oral dose, should not exceed 75 micrograms/mL. Flucytosine should be avoided among children with severe renal impairment **(EIII)**.

Fluconazole and the other azoles have relatively low rates of toxicity, but their potential drug interactions can limit their use. Because of their ability to inhibit the CYP450-dependent hepatic enzymes, the potential for drug interactions, particularly with antiretroviral drugs, should be carefully evaluated before initiation of therapy **(AIII)**.

Immune Reconstitution Inflammatory Syndrome

Patients who develop cryptococcal IRIS are more likely to be severely immunocompromised with disseminated infection and to have initiated potent antiretroviral therapy soon after diagnosis of cryptococcal disease; in antiretroviral-naïve patients newly diagnosed with cryptococcal meningitis, it may be prudent to delay the initiation of potent antiretroviral therapy until the end of the first 2 weeks of induction therapy **(CIII)**.

IRIS related to cryptococcosis can present within weeks (e.g., meningitis) or months (e.g., lymphadenitis) after initiating HAART. Symptoms of meningitis are similar to those described at presentation. In one study, about 30% of all HIV-infected adults hospitalized for infection with *C. neoformans* who received HAART were readmitted with symptoms attributed to an inflammatory response. Of the 18 patients with *C. neoformans*-related IRIS in the cited study, 17 had culture-negative meningitis, and most cases arose during the first 30 days after initiation of HAART. The most common presentation of late cryptococcal IRIS is lymphadenitis, particularly mediastinal lymphadenitis.

The optimal management of cryptococcal IRIS has not been defined. Patients not already on antifungal therapy should have the antifungal therapy initiated and antiretroviral therapy should be continued **(AII)**. While many cases resolve

spontaneously, anti-inflammatory therapy (e.g., short-course corticosteroids) has also been used by some experts in patients with severely symptomatic IRIS **(BIII)**.

Management of Treatment Failure

Treatment failure is defined as clinical deterioration despite appropriate therapy, including management of intracranial pressure; lack of improvement in signs and symptoms after 2 weeks of appropriate therapy; or relapse after an initial clinical response. Differentiating IRIS from treatment failure is important because treatment approaches and outcomes differ. Optimal management of patients with treatment failure is not known. If cultures are positive at the time of treatment failure, evaluation of antifungal susceptibilities may be considered, although fluconazole resistance with *C. neoformans* is rare in the United States (although more common in some international settings). Patients failing initial azole-based therapy should be switched to amphotericin B-based therapy, ideally in combination with flucytosine **(BIII)**; the possibility of drug interactions resulting in subtherapeutic azole levels (e.g., concurrent rifampin use or other drugs metabolized by the liver) should be explored. Use of liposomal amphotericin B should be considered, as one study suggests improved efficacy in CSF sterilization with liposomal preparations than with standard amphotericin B **(AII)**. Some data from HIV-infected adults indicate higher doses (e.g., 400–800 mg/day) of fluconazole in combination with flucytosine can also be considered for salvage therapy **(BII)**. Clinical experience with new antifungal agents in the management of cryptococcosis is limited. A few patients with cryptococcal infections refractory or intolerant to standard antifungal therapy have been treated with posaconazole or voriconazole with variable success. Currently available echinocandins do not have clinical activity against cryptococcal infections and should not be used.

Prevention of Recurrence

Patients who have completed initial therapy for cryptococcosis should receive suppressive treatment (i.e., secondary prophylaxis or chronic maintenance therapy) **(AI)**. Fluconazole **(AI)** is superior and preferable to itraconazole **(BI)** for preventing relapse of cryptococcal disease. Suppressive therapy typically is continued long term. Criteria for considering discontinuation of secondary prophylaxis are discussed below.

Discontinuing Secondary Prophylaxis

Until recently lifelong secondary prophylaxis was typically recommended. The safety of discontinuing secondary prophylaxis for cryptococcosis after immune reconstitution with HAART has not been studied in children, and decisions in this regard are to be made on a case-by-case basis. Adult patients at apparent low risk for recurrence of cryptococcosis have successfully completed a course of initial therapy, remain asymptomatic with regard to signs and symptoms of cryptococcosis, and have a sustained (≥6 months) increase in their CD4 counts to ≥200 cells/mm^3 after HAART. In light of these observations and inference from data regarding discontinuing secondary prophylaxis for other OIs during advanced HIV disease in HIV-infected adults, discontinuing chronic suppressive therapy for cryptococcosis (after being on it for ≥6 months) can be considered for asymptomatic pediatric patients aged ≥6 years, on HAART, and with sustained

(≥6 months) increase in their CD4 counts to >200 cells/mm^3 **(BII)**. Suppressive therapy should be reinitiated if the CD4 count decreases to <200 cells/mm^3 **(AIII)**.

Fungal Infections: Histoplasmosis

Prevention Recommendations

Preventing Exposure

Most infections occur without a recognized history of exposure to a high-risk site or activity. Therefore, complete avoidance of exposure in endemic regions is not possible. Sites and conditions commonly implicated in high-risk exposure and point source outbreaks include soil contaminated with bird or bat droppings, older urban and rural structures, decaying vegetation/trees, and caves. Dry and windy conditions, excavation, demolition, and gardening/agricultural activities predispose to aerosolization of spores. If avoidance of these activities is not feasible, reducing the release of spores by wetting soil, renovation sites, etc., and using protective respiratory devices may reduce the likelihood of infection.

Preventing First Episode of Disease

Prophylaxis with itraconazole is recommended for HIV-infected adults whose CD4 count is <150 cells/mm^3 and who reside in highly endemic areas (i.e., incidence of histoplasmosis is >10 cases per 100 patient-years) and/or in instances in which there is high-risk occupational exposure. Prophylaxis had no effect on survival. Given the low incidence of histoplasmosis in pediatric HIV-infected patients, possibility of drug interaction, potential antifungal drug resistance, and cost, routine use of antifungal medications for primary prophylaxis of histoplasma infections in children is not recommended.

Discontinuing Primary Prophylaxis

Although studies have not been done to support the safety of discontinuing primary prophylaxis, the safety of discontinuing suppressive therapy (secondary prophylaxis) for HIV-infected adults with CD4 counts >150 cells/mm^3 has been demonstrated; treatment should be resumed if CD4 count falls below this threshold and the patient continues to reside in an area in which the threshold of >10 cases per 100 patient-years is exceeded. Prophylaxis is not recommended for HIV-infected children.

Treatment Recommendations

Treatment of Disease

Progressive disseminated histoplasmosis (PDH) is fatal without treatment. Therapy with either amphotericin B deoxycholate or itraconazole is highly effective. The clinical response to amphotericin B is faster and it is preferred for the initial treatment of severe infections **(AI)**. Although amphotericin B may be used as monotherapy for an extended length of time, it is now more commonly used as induction therapy and is followed by long-term treatment with

itraconazole. Itraconazole is the azole preferred for the treatment of histoplasmosis. Trials of therapy and the effectiveness of primary and secondary prophylaxis have been evaluated in HIV-infected adults. Recommendations for HIV-infected children are derived from these data and from anecdotal experience in children. However, since there are important differences in the management of children with PDH, consultation with experts should be considered.

The dosage of liposomal amphotericin B for children is 3–5 mg/kg/day. Other less costly or better tolerated lipid formulations may be substituted for the liposomal product. Amphotericin B deoxycholate, at a dose of 1 mg/kg/day, is better tolerated by children than it is by adults, is effective, and may be used when cost of the lipid preparations is a consideration.

Itraconazole is usually well tolerated in children. Itraconazole has a long half-life and steady-state is not reached until 2 weeks. The interval needed to achieve desired serum concentrations can be shortened if the recommended dose is given three times daily for the initial 3 days of therapy ("loading dose"); the recommended dose given twice daily should be started thereafter. Itraconazole solution is preferred to the capsule formulation since it is better absorbed and serum concentrations are 30% higher than those achieved with the capsules. Since there is substantial intersubject variability in absorption of itraconazole, serum concentrations should be measured to ensure effective levels of drug, monitor changes in dosage, and assess compliance **(BIII)**. The minimal inhibitory concentration (MIC) of *H. capsulatum* is 0.01 microgram/mL and, though minimally effective serum concentrations have not been determined, a serum concentration of 1.0 microgram/mL is recommended; dosage should be reduced if concentrations exceed 10 micrograms/mL.

Fluconazole has been used successfully and is an alternative for patients with mild histoplasmosis who are intolerant of itraconazole or in whom desired serum levels cannot be attained. However, fluconazole is both less effective than itraconazole and has been associated with the development of drug resistance **(CII)**. Ketoconazole is infrequently used due to its adverse reactions; it has been demonstrated to be effective in mild infections, excluding disseminated infection, and may be considered since it is much less costly than the other azoles.

Acute Primary Pulmonary Histoplasmosis

Exposure to a large fungal inoculum may result in fever, dyspnea, and diffuse pulmonary infiltrates. All patients, irrespective of immune status, should receive treatment with antifungal agents **(AIII)**. For severe or moderately severe symptoms, amphotericin B should be given for 1 to 2 weeks; amphotericin B deoxycholate is preferred as it is well tolerated in children **(AIII)**. Following clinical improvement, patients with intact immunity should receive itraconazole, beginning with a loading dose (see above) for the first 3 days, then followed by the recommended dose given twice daily for at least 12 weeks **(AIII)**; adults with CD4 counts of <150 cells/mm^3 and, by extrapolation, HIV-infected children with severe immunosuppression (e.g., CD4 <15% or <150 cells/mm^3 in children aged ≥6 years) should receive itraconazole for 12 months **(AIII)**. Urine antigen is usually elevated in these settings and should be monitored to gauge clinical response and, following treatment, identify relapse.

HIV-infected children, particularly those with functional cellular immunity, will occasionally present with fever associated with mild primary pulmonary infection, often associated with mildly to moderately elevated histoplasma urine antigen. While such illnesses may be self-limited by an effective cellular immune response, it may be prudent to treat with itraconazole for 12 weeks while following histoplasmal urine antigen concentrations to ensure that they decrease **(BIII)**.

Severe/Moderately Severe PDH

Based on data from HIV-infected adults, HIV-infected children with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous amphotericin B formulation for ≥2 weeks or until they clinically improve, followed by itraconazole for 12 months **(AI)**. In HIV-infected adults, moderately severe to severe PDH responds more favorably (88% vs 64%) and results in lower mortality (2% vs 13%) to liposomal amphotericin B than to the deoxycholate formulation **(AI)**. Following a favorable clinical response, amphotericin B is discontinued and followed by "step-down" therapy with itraconazole for 12 months **(AII)**. A loading dose (see above) of itraconazole should be used for the initial 3 days. Should itraconazole not be well tolerated, a 4- to 6-week course of amphotericin B should be used and histoplasma urine antigen followed **(AIII)**.

Although therapeutic trials of amphotericin B deoxycholate used for the treatment of PDH in HIV-infected children have not been performed, this formulation is very effective for treating severe PDH in infants, including those with CNS infection, and in children with other primary or acquired immunodeficiency states. Amphotericin B deoxycholate is better tolerated by children than by adults, and it is less costly than other formulations. It may be used if cost or availability of lipid formulations precludes their use **(AIII)**.

Mild-to-Moderate PDH

Mild-to-moderate PDH in adults without signs of CNS infection has been shown to respond favorably in 80%–100% of patients treated with itraconazole monotherapy for 12 months **(AII)**. This regimen is also recommended for HIV-infected children with mild-to-moderate PDH **(AII)**. A loading dose of itraconazole (see above) should be given at the onset of treatment and serum concentrations monitored.

CNS Infection

CNS infection that accompanies PDH is expected to respond to the regimen recommended for moderately severe to severe PDH. Isolated CNS infection is unusual in children. In adults, frequent failure and relapse are common and aggressive therapy is recommended. Liposomal amphotericin B is preferred for CNS disease in children and adults since it achieves higher concentrations in the brain **(AII)**; penetration into the CSF is poor with all formulations. The deoxycholate formulation is an alternative. Amphotericin should be given for 4 to 6 weeks. Thereafter, the child should receive a loading dose of itraconazole and continuation of itraconazole for 12 months **(AII)** and until CSF abnormalities, including histoplasmal antigen, have resolved. Antigen levels should be followed and dose adjusted to ensure optimal serum concentrations.

Asymptomatic Histoplasma Granuloma

In asymptomatic HIV-infected children who have intact cellular immunity and have resided in an endemic area, the presence of a typical granuloma in a chest radiograph should prompt evaluation of both histoplasmal urine antigen and CF and immunodiffusion (ID) antibody. If any of these tests are positive, treatment with itraconazole for 12 weeks is prudent **(BIII)**. If negative, therapy need not be used and clinical follow-up is recommended. In either instance, histoplasmal urine antigen testing should be considered if unexplained fever or other systemic symptoms occur.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

In manifestations of histoplasmosis in which antigenuria is demonstrated, antigen levels should be monitored during therapy and for a year thereafter to identify relapse **(AIII)**. Following a recommended course of therapy and, in the absence of symptoms, low-level, stable antigenuria may not constitute a basis for prolonging the recommended course of therapy. Serum levels of itraconazole should be monitored in patients receiving treatment.

Adverse effects of amphotericin B are primarily nephrotoxicity; permanent nephrotoxicity is related to cumulative dose. Infusion-related fevers, chills, nausea, and vomiting can occur, although they are less frequent in children than in adults. Renal dysfunction and electrolyte imbalances are its primary toxicities; these parameters should be monitored during therapy.

Itraconazole, as other azoles, has relatively low rates of toxicity. GI upset is seen occasionally and its principal toxicity is hepatic. The azole drugs inhibit CYP450-dependent hepatic enzymes so that drug interactions, particularly with antiretroviral drugs, should be carefully evaluated before initiation of therapy.

IRIS caused by an inflammatory response to histoplasmosis unmasked by HAART-induced improvement in cellular immunity is unusual and symptoms are often mild. In the event of its occurrence, antiretroviral therapy should be continued along with antifungal therapy.

Management of Treatment Failure

Both voriconazole and posaconazole have been used successfully in a small number of refractory cases in adults. Since little experience has been reported using the newer azoles and there are only limited data on use of these agents in children, expert consultation is recommended for cases refractory to first-line agents.

Prevention of Recurrence

Children responding well after completion of initial amphotericin B treatment should be continued on oral itraconazole maintenance therapy for at least 1 year **(AII)**. Longer term suppressive therapy with itraconazole may be required in HIV-infected children who are severely immunosuppressed (i.e., CD4 <15% or

<150 cells/mm^3 in children aged ≥6 years) and patients who experience relapse despite receipt of appropriate therapy **(AII)**. Fluconazole is less effective than itraconazole **(CII)** and there is only limited experience in children with voriconazole.

Discontinuing Secondary Prophylaxis

Though not examined in children, based on data from a clinical trial evaluating discontinuation of treatment in adults with immune restoration on HAART, discontinuation of itraconazole is recommended in adults if itraconazole has been received for ≥1 year, blood cultures are negative, histoplasmal serum antigen is <2 ng/mL, CD4 counts are >150 cells/mm^3, and the patient is compliant with HAART therapy **(AI)**. Extrapolating these recommendations to HIV-infected children on HAART with immune restoration (i.e., CD4 >15% or CD4 >150 cells/mm^3 in children aged ≥6 years) seems reasonable **(CIII)**. Treatment should be resumed if these parameters are not met. Chronic suppressive therapy is recommended for patients who relapse despite appropriate treatment.

Fungal Infections: *Pneumocystis* Pneumonia

Prevention Recommendations

Preventing Exposure

The need for contagious isolation of hospitalized *Pneumocystis jirovecii* pneumonia (PCP) cases has been neither demonstrated nor discounted. Clearly, there is no need to isolate PCP cases from individuals with normal immune responses and from immunocompromised high-risk patients who are receiving PCP prophylaxis. Under unusual circumstances where prophylaxis cannot be given, room isolation of either the infected or the susceptible patient may be warranted **(CIII)**.

Preventing First Episode of Disease

Chemoprophylaxis is highly effective in the prevention of PCP. Criteria for its use are based on the patient's age and CD4 count or percentage **(AII)**. Prophylaxis is recommended for all HIV-infected children aged ≥6 years with CD4 counts <200 cells/mm^3 or CD4 <15%, for children aged 1 to 5 years with CD4 counts of <500 cells/mm^3 or CD4 <15%, and for all HIV-infected infants aged <12 months regardless of CD4 count and percentage.

Infants born of HIV-infected mothers should be considered for prophylaxis beginning at 4 to 6 weeks of age. HIV-infected infants should be given prophylaxis until 1 year of age, at which time reassessment is made based on the age-specific CD4 count or percentage thresholds mentioned above **(AII)**. Infants with indeterminate HIV infection status should receive prophylaxis until they are determined to be HIV uninfected or presumptively uninfected with HIV. Prophylaxis is not recommended for infants who meet criteria for HIV-uninfected and presumptively uninfected with HIV status. In nonbreastfeeding infants with no positive HIV virologic test results, presumptive exclusion of HIV infection can be based on two negative virologic test results, one obtained at ≥2 weeks and one obtained at ≥4 weeks of age; one negative virologic test result obtained at ≥8

weeks of age; or one negative HIV antibody test result obtained at ≥6 months of age. Definitive exclusion of HIV infection is based on two negative virologic test results, one obtained at ≥1 month of age and one obtained at ≥4 months of age, or two negative HIV antibody test results from separate specimens obtained at ≥6 months of age. For both presumptive and definitive exclusion of infection, the child should have no other laboratory (e.g., no positive virologic test results) or clinical (e.g., no AIDS-defining conditions) evidence of HIV infection.

Four drug regimens have been found effective and relatively safe for the prevention of PCP in high-risk HIV-infected children and adults:

Trimethoprim-sulfamethoxazole (TMP-SMX) (cotrimoxazole) is the drug of choice for prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum **(AI)**. Trimethoprim alone has little, if any, anti-*Pneumocystis* activity but it enhances the activity of the sulfonamide. The prophylactic dosage is 150 mg/meter^2 body surface area/day trimethoprim (TMP) and 750 mg/meter^2 body surface area/day sulfamethoxazole (SMX) (approximately 5.0 mg/kg/day TMP and 25 mg/kg/day SMX) given orally in equally divided doses twice a day 3 consecutive days per week. The total daily dose should not exceed 320 mg TMP and 1,600 mg SMX. For patients with impaired renal function, a reduced dose may be necessary.

Alternatively, TMP-SMX may be administered daily 7 days a week **(AI)**. Note that TMP-SMX is also effective in the prevention of toxoplasmosis and some bacterial infections (*Salmonella*, *Haemophilus*, *Staphylococcus*, and others).

Dihydropteroate synthase (DHPS) gene mutations in *Pneumocystis* from humans have been observed with TMP-SMX and dapsone prophylaxis, suggestive of possible drug resistance, but studies for clinical correlates have not provided conclusive results. More apparent is the association of prolonged TMP-SMX prophylaxis for PCP with the emergence of selective pressure resistance of clinically important bacterial species to TMP-SMX, a point to be considered in the management of bacterial infections occurring in patients receiving prophylaxis.

Other effective and safe prophylaxis regimens are available for those who are unable to take TMP-SMX. A second choice would be either atovaquone or dapsone **(BI)**. Atovaquone is effective and safe but expensive. Dapsone is effective and cheap but associated with more serious adverse effects than atovaquone.

Atovaquone is administered with a meal as an oral yellow suspension in a single dose of 30 mg/kg/day for patients 1 to 3 months and >24 months of age, and 45 mg/kg/day for infants aged 4 to 24 months. Unlike TMP-SMX, atovaquone has no antibacterial activity, but is effective against *Toxoplasma gondii*. Azithromycin in a single dose of 5.0 mg/kg/day has been used to supplement atovaquone for greater broad-spectrum prophylaxis. The randomized, double-blind, placebo-controlled study PACTG 254 compared TMP-SMX and atovaquone plus azithromycin for a period of 3 years (median) in 366 HIV-infected children qualifying for PCP prophylaxis. Results showed atovaquone-azithromycin to be as effective as TMP-SMX for the prevention of serious bacterial infections as well as PCP. Dapsone may be given on a daily or weekly schedule as 2.0 mg/kg/day (maximum total dose of 100 mg/day) or 4.0 mg/kg/week (maximum total dose of 200 mg/week) orally. Approximately two-thirds of patients intolerant to TMP-SMX

can take dapsone successfully. Studies in adults show dapsone is as effective as atovaquone or aerosolized pentamidine but slightly less effective than TMP-SMX.

Aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone and are old enough to use nebulization with a Respirgard II® nebulizer (Marquest, Englewood, CO) **(BI)**. The dosage for all ages is 300 mg once a month. Adverse reactions among HIV-infected children include cough, sneezing, and bronchospasm.

Pyrimethamine-sulfadoxine (Fansidar®) is also recognized as an effective prophylaxis regimen in adults **(CIII)**. Although this drug was found to be effective in the prevention of PCP in Iranian orphanages in the 1960s, it has not been evaluated adequately among HIV-infected pediatric patients.

The use of intravenous pentamidine is not recommended for prophylaxis **(EIII)**.

Discontinuing Primary Prophylaxis

Studies of HIV-infected adults and children following immune reconstitution after receipt of HAART demonstrate acceptable low risks for PCP after discontinuation of prophylaxis. Data from the PACTG 1008 study evaluated 235 HIV-infected children and adolescents on antiretroviral therapy who received PCP prophylaxis ≥6 months and achieved CD4 percentages of ≥20% for patients aged >6 years and ≥25% for patients aged 2 to 6 years, after which the prophylaxis was stopped. During the median follow-up period of 2.5 years (547 person-years), no cases of PCP occurred; 9.4% of patients enrolled required reinstitution of PCP prophylaxis during the observation period. These data along with those from adult studies support the expectation for very low risk of PCP after discontinuation of prophylaxis for children who have achieved immune reconstitution.

It is recommended that consideration be given to discontinuation of PCP prophylaxis for HIV-infected children when, after receiving HAART for ≥6 months, CD4 percentage is ≥15% or CD4 count is ≥200 cells/mm^3 for patients aged >6 years **(BII)** and CD4 percentage is ≥15% or CD4 count is ≥500 cells/mm^3 for patients aged 1 to 5 years **(BII)** for >3 consecutive months. Subsequently, the CD4 percentage and count should be re-evaluated at least every 3 months and prophylaxis reinstituted if the original criteria for prophylaxis are reached **(BIII)**. PCP prophylaxis is not to be discontinued in HIV-infected infants aged <1 year.

Treatment Recommendations

Treatment of Disease

TMP-SMX is the recommended treatment for PCP **(AI)**. The dose for HIV-infected children aged >2 months is 15 – 20 mg/kg/day of the TMP component and 75–100 mg/kg/day of the SMX component administered intravenously in three to four divided doses, with the dose infused over 1 hour for 21 days **(AI)**. As the acute pneumonitis subsides, children with mild-to-moderate disease who do not have malabsorption or diarrhea can be administered oral treatment with the same dose of TMP-SMX in three to four divided doses to complete a 21-day course **(AII)**.

Effective therapeutic serum concentrations of 5–10 micrograms/mL TMP can be achieved with the recommended dose given orally in HIV-infected children.

Intravenous pentamidine isethionate once daily is recommended for patients intolerant of TMP-SMX or who demonstrate clinical treatment failure after 5 to 7 days of TMP-SMX therapy **(AI)**. No evidence exists for synergistic or additive effects on efficacy of these agents; therefore, because of potential increased toxicity, their combined use is not recommended **(DIII)**. Among patients with clinical improvement after 7 to 10 days of intravenous therapy with pentamidine, an oral regimen (e.g., atovaquone or trimethoprim/dapsone) might be considered to complete a 21-day course **(BIII)**.

Atovaquone is an alternative for treatment of mild to moderately severe PCP in adults **(BI)**. Therapeutic data are limited for children but the dosage of 30–40 mg/kg/day in two divided doses given orally is established for individuals <3 months and ≥24 months of age. Children aged 3 to 24 months require a higher dosage of 45 mg/kg/day **(AII)**. The dose for adolescents and adults is 750 mg twice daily. Food increases the bioavailability of atovaquone to ≥3-fold more than that achieved with the fasting state. Atovaquone concentration is increased with coadministration of fluconazole and prednisone and decreased by coadministration with acyclovir, opiates, cephalosporins, rifampin, and benzodiazepines.

Dapsone/trimethoprim is effective in the treatment of mild-to-moderate PCP among adults **(BI)**; data on toxicity and efficacy among children are limited. The dose of dapsone for adolescents and adults is 100 mg (total dose) orally once daily and trimethoprim 15 mg/kg/day divided into three daily doses administered for 21 days. Among children aged <13 years, a dapsone dose of 2 mg/kg/day is required to achieve therapeutic levels in children **(AII)**. The pediatric dose of TMP is 15 mg/kg/day divided into three daily doses. Dapsone is less effective than the combination.

Clindamycin/primaquine has been used for treatment of mild-to-moderate PCP among adults **(BI)**; data for children are not available. Primaquine is contraindicated for patients with glucose-6-dehydrogenase deficiency due to the possibility of inducing hemolytic anemia. Dose information for treatment of PCP is available only for adults. For patients weighing >60 kg, clindamycin 600 mg intravenously every 6 hours for 10 days, then 300–450 mg orally every 6 hours to complete 21 days of treatment is recommended. Primaquine is administered as 30 mg of base orally for 21 days. Dosing for children is based on use of these drugs for treatment of other infections: the usual pediatric dose of clindamycin for treatment of bacterial infection is 10 mg/kg/dose every 6 hours, and the pediatric dose of primaquine equivalent to an adult dose of 20 mg base (when used for malaria) is 0.3 mg/kg/day of the base.

On the basis of studies in adults, a short course of corticosteroids is recommended in some cases of PCP of moderate or severe intensity, starting within 72 hours of diagnosis **(AI)**. Pediatric studies have indicated a reduction in acute respiratory failure, a decrease in the need for ventilation, and a decrease in mortality with early use of corticosteroids in HIV-infected children with PCP. Indications for corticosteroid treatment include a PaO_2 value of <70 mmHg or an alveolar-arterial gradient of >35 mmHg. Doses for children vary between studies. A commonly used scheme is prednisone on Days 1 to 5, 1 mg/kg/dose twice daily; Days 6 to

10, 0.5 mg/kg/dose twice daily; and Days 11 to 21, 0.5 mg/kg once daily. Alternative regimens include: (1) adult dosage prednisone on Days 1 to 5, 40 mg twice daily; Days 6 to 10, 40 mg once daily; Days 11 to 21, 20 mg once daily; and (2) methylprednisolone (intravenous) on Days 1 to 7, 1 mg/kg/dose every 6 hours; Days 8 to 9, 1 mg/kg/dose twice daily; Days 10 to 11, 0.5 mg/kg/dose twice daily; Days 12 to 16, 1 mg/kg once daily.

Some case reports have documented improved pulmonary function with use of surfactant in cases of severe disease (e.g., respiratory distress syndrome with established respiratory failure requiring ventilation) **(CIII)**. Alterations in surfactant function and composition have been demonstrated in HIV-infected patients with PCP. No therapeutic schemes have been established.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Clinical parameters to monitor the status of disease include temperature, respiratory rate, arterial oxygen saturation, and chest radiograph. Clinical improvement can be expected at around a mean of 4.5 ± 2.5 days and radiographic improvement at around 7.7 ± 4.5 days.

IRIS has been less frequently associated with *Pneumocystis* infection (2% of 44 adults with IRIS) than several other OIs in HIV-infected adults and children. Whether this low rate is related to PCP prophylaxis is not known.

In children, adverse reactions to TMP-SMX include rash (mild maculopapular in most cases but rarely erythema multiforme and Stevens-Johnson syndrome), hematologic abnormalities (e.g., neutropenia, thrombocytopenia, megaloblastic or aplastic anemia), GI complaints (usually mild), hepatitis, and renal disorders (e.g., interstitial nephritis). Data from a PACTG study of HIV-infected children at high-risk for PCP receiving TMP-SMX for a median of 3 years showed 28% had a rash, 9.3% neutropenia, 8.8% thrombocytopenia, and 2.2% anemia. None were fatal or nonreversible reactions. Some very mild reactions will resolve while the drug is continued. With any significant adverse effect, TMP-SMX should be withheld until the reaction has subsided. Unless the reaction has been life-threatening, TMP-SMX prophylaxis can be resumed, preferably by beginning with low desensitizing daily doses and gradually increasing to full doses **(BII)**. In adults, 75% of patients affected are able to tolerate rechallenge with TMP-SMX. The overall frequency of adverse reactions appears to be lower among HIV-infected children than adults; approximately 15% of children have substantial adverse reactions to TMP-SMX. If an urticarial rash or Stevens-Johnson syndrome occurs, TMP-SMX should be discontinued and not readministered **(EIII)**.

The most common adverse drug reaction to pentamidine isethionate is renal toxicity, which usually occurs after 2 weeks of therapy and can be averted by adequate hydration and careful monitoring of renal function and electrolytes. Severe hypotension (particularly if infused rapidly), prolonged QT interval (torsades de pointes), and cardiac arrhythmias can occur. Hypoglycemia (usually after 5 to 7 days of therapy) or hyperglycemia, hypercalcemia, hyperkalemia, pancreatitis, and insulin-dependent diabetes mellitus have also been reported. A metallic or bitter taste may be experienced. Serious adverse reactions to pentamidine have been reported in approximately 17% of children receiving the

drug. Care should be taken to avoid administering this drug with other nephrotoxic drugs (e.g., aminoglycosides, amphotericin B, cisplatin, or vancomycin) and with agents associated with pancreatitis (e.g., didanosine).

With dapsone and trimethoprim, the primary adverse reaction is reversible neutropenia; other reactions include skin rashes, elevated serum transaminases, methemoglobinemia, anemia, and thrombocytopenia. Dapsone is the problematic component of the combination and accounts for most of the adverse reactions.

Skin rashes (10%–15%), nausea, and diarrhea may occur with atovaquone administration. Transient increase in liver enzymes may occur. No serious toxicity or fatality has been demonstrated from the use of atovaquone in adults or children.

Adverse reactions to clindamycin/primaquine include skin rash, nausea, and diarrhea.

Management of Treatment Failure

There can be an initial early and reversible deterioration in the first 3 to 5 days of therapy, likely due to an inflammatory reaction to antibiotic-induced killing of the organism in the lungs, so an adequate trial of therapy is needed before switching drugs for lack of clinical improvement. Clinical failure is defined by the lack of improvement or worsening of respiratory function documented by arterial blood gases after at least 4 to 8 days of anti-PCP treatment. Other concomitant infections need to be excluded as a cause of clinical failure. With evidence of treatment failure after the use of TMP-SMX, drugs can be changed. If tolerated, pentamidine isethionate is the drug of next choice **(BII)**. No evidence exists for synergistic or additive therapeutic effects; therefore, because of potential increased toxicity their combination is not recommended.

Prevention of Recurrence

It is important to note that none of the drugs administered for the treatment and prevention of PCP completely eradicates *Pneumocystis* and that prophylaxis is effective only while the selected drug is administered. Patients who have experienced an episode of PCP should have prophylaxis administered continuous with completion of treatment **(AI)**.

Discontinuing Secondary Prophylaxis

In most patients secondary prophylaxis may be discontinued using the same criteria as for the discontinuation of primary prophylaxis. Thus, consideration may be given to discontinuation of PCP prophylaxis for HIV-infected children when, after receiving HAART for ≥6 months, CD4 percentage is ≥15% or CD4 count is ≥200 cells/mm^3 for patients aged >6 years **(BII)** and CD4 percentage is ≥15% or CD4 count is ≥500 cells/mm^3 for patients aged 1 to 5 years **(BII)** for >3 consecutive months. Subsequently, the CD4 percentage and CD4 count should be re-evaluated at least every 3 months and prophylaxis reinstituted if the original criteria for prophylaxis are reached or if PCP recurs **(BIII)**. PCP prophylaxis is not to be discontinued in HIV-infected infants <1 year. Individuals who present with

clinical signs and symptoms compatible with PCP after discontinuation of prophylaxis should be evaluated thoroughly despite normal or high CD4 counts or percentages **(BII)**.

Definitions:

Rating Scheme for Prevention and Treatment Recommendations	
A	Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. **Should always be offered.**
B	Moderate evidence for efficacy - or strong evidence for efficacy but only limited clinical benefit - supports recommendation for use. **Should generally be offered.**
C	Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequence (e.g., drug toxicity, drug interactions) or cost of the treatment under consideration. **Optional.**
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should generally not be offered.**
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should never be offered.**
Quality of Evidence Supporting the Recommendation	
I	Evidence from at least one randomized, controlled trial.
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies. Or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for most recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate prevention and treatment of fungal infections in human immunodeficiency virus (HIV)-exposed and HIV-infected children

POTENTIAL HARMS

Adverse Drug Effects and Drug Interactions

Major toxicities and interactions of the drug preparations used in treatment of opportunistic infections are discussed in the Major Recommendations section of this summary and in Table 5 in the original guideline document. Drug interactions of clinical significance are discussed in Table 6 in the original guideline document.

CONTRAINDICATIONS

CONTRAINDICATIONS

A list of drug contraindications for prevention of drug interactions is provided in Table 6 of the original guideline document.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Treatment of opportunistic infections is an evolving science, and availability of new agents or clinical data on existing agents might change therapeutic options and preferences. As a result, these recommendations will need to be periodically updated.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Fungal infections. In: Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), HIV Medicine Association of the Infectious Diseases Society of America, Pediatric Infectious Diseases Society, American Academy of Pediatrics. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2008 Jun 20. p. 39-73.

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Centers for Disease Control and Prevention (CDC), their planners, and their content specialists wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. This report does not include any

discussion of the unlabeled use of a product or a product under investigational use.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 3;53(RR-14):1-92. [422 references]

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site.

The guideline is also available for Palm OS or Pocket PC download from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 20, 2004. This summary was updated on January 21, 2005, following the release of a public health advisory from the U.S. Food and Drug Administration regarding the use of nevirapine. This summary was most recently updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisories on Sustiva (efavirenz) and COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI Institute on October 3, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Rocephin (ceftriaxone sodium). This summary was updated by ECRI Institute on July 28, 2008 following the U.S. Food and Drug Administration advisory on fluoroquinolone antimicrobial drugs. This NGC summary was updated by ECRI Institute on August 24, 2009.

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